EXHIBIT A

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 11 Cases*	

GENERAL EXPERT REPORT OF BRUCE S. KAHN, MD

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., **PELVIC REPAIR SYSTEM** **PRODUCTS LIABILITY LITIGATION**	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

GENERAL EXPERT REPORT OF

BRUCE S. KAHN, MD

GENERAL REPORT RE: THE TVT DEVICE

I. Background

I graduated from the University of California Irvine with a degree in Biological Sciences in 1984. I then earned a Master's degree in Physiology in 1986 and Doctor of Medicine degree in 1990 from Georgetown University in Washington, D.C. I completed internship in internal medicine at St. Joseph Hospital & Medical Center in Chicago, IL in 1991 and began residency training in Radiation Oncology at George Washington University in Washington, DC. I then switched career paths and completed residency training in obstetrics & gynecology at Cedars-Sinai Medical Center in Los Angeles (1992-93) and Abington Memorial Hospital near Philadelphia, PA in (1993-96).

Following residency training, I was commissioned as a Lieutenant Commander in the U.S. Naval Reserve and served as a Staff Obstetrician-Gynecologist and Clinical Instructor at the Naval Medical Center San Diego from 1996-1998. I was then recruited to the faculty of the Department of Reproductive Medicine at the University of California San Diego where I served as an Assistant Clinical Professor from 1998-1999. I then accepted a position in the Division of Gynecologic Surgery at Scripps Clinic in San Diego CA and have worked there since 1999.

My practice is primarily focused on providing clinical patient care, but I am also involved in clinical teaching and research. I created and continue to direct a rotation at Scripps clinic for residents from the Department of Obstetrics and Gynecology at the Naval Medical Center San Diego. Related to this work, I hold a faculty appointment as an Adjunct Clinical Professor in the Department of Obstetrics & Gynecology at the Uniformed Services University of the Health Sciences in Bethesda, MD. I also created and direct the Scripps Fellowship in Minimally Invasive Gynecologic Surgery (FMIGS). Additionally, I lecture on topics related to gynecology nationally and internationally. I am also involved in several clinical research projects at any one time. My research interests relevant to this case include work on pelvic organ prolapse, urinary incontinence, and pelvic pain problems including interstitial cystitis and endometriosis.

I am board certified in Obstetrics & Gynecology and was among the first group of surgeons in the country to attain sub-specialty certification in Female Pelvic Medicine & Reconstructive Surgery (Urogynecology) in 2013. I am a fellow of the American College of Obstetrician-Gynecologists (ACOG), and a member of the American Association of Gynecologic Laparoscopists (AAGL) and the American Urogynecologic Society (AUGS).

During residency, I was trained in and gained experience with a variety of surgical procedures for the treatment of urinary incontinence in women including the Kelly plication, Marshall-Marchetti-Krantz and Burch procedures, as well as autologous facial slings and needle suspension (Pereyra) procedures.

In the years following residency, I continued to evaluate and treat patients for urinary incontinence symptoms. I studied reports on the treatment of stress urinary incontinence with retropubic mesh slings. In approximately 2000, I performed my first retropubic sling procedures using Gynecare's TVT Tension Free support system. During my career, I have continued to

study, attend meetings, attend and help with training labs for the use and placement of mesh slings for the treatment of stress urinary incontinence. More recently, I have been a site principal investigator on two different FDA mandated "522" trials, one on the use of single-incision mesh slings for urinary incontinence and another on the use of mesh for the treatment of pelvic organ prolapse procedures.

I am being compensated at a rate of $550 per hour for my work on this case. I have not testified as an expert witness in the previous four years in trial or deposition.

II. Urinary Incontinence

Urinary incontinence is a common condition in women. Approximately 25% of young women, 44–57% of middle-aged and postmenopausal women, and 75% of older women experience some involuntary urine loss. The estimated direct cost of urinary incontinence care in the United States is $19.5 billion (Carls C. The prevalence of stress urinary incontinence in high school and college-age female athletes in the midwest: implications for education and prevention. Urol Nurs 2007;27:21–4, 39; Kinchen KS, Lee J, Fireman B, Hunkeler E, Nehemiah JL, Curtice TG. The prevalence, burden, and treatment of urinary incontinence among women in a managed care plan. J Womens Health (Larchmt) 2007;16:415–22; Boyington JE, Howard DL, Carter-Edwards L, Gooden KM, Erdem N, Jallah Y, et al. Differences in resident characteristics and prevalence of urinary incontinence in nursing homes in the southeastern United States. Nurs Res 2007;56:97–107; Shamliyan T, Wyman J, Kane RL. Nonsurgical treatments for urinary incontinence in adult women: diagnosis and comparative effectiveness. Comparative Effectiveness Reviews No. 36. Rockville (MD): Agency for Healthcare Research and Quality; 2012.) Incontinence can be considered to be a subjective symptom (described by the patient), an objective finding on examination (the patient coughs with a full bladder and urine is observed coming from the urethra), or a condition that is determined by subjective and objective findings, including urodynamic evaluation. Accordingly, outcome tools can be subjective (including bladder diaries and validated surveys to determine quality-of-life scores, severity of incontinence, and treatment satisfaction) or objective (weighing a patient's incontinence pads, cough stress testing to observe incontinence, and other complex urodynamic tests). At present, there is no single outcome that adequately measures success after treatment of urinary incontinence.

Despite the prevalence of urinary incontinence, many women are hesitant to seek care or discuss their symptoms with a physician. In a survey of women in the United States, only 45% of women who reported at least weekly urine leakage sought care for their incontinence symptoms. (Anger JT, Saigal CS, Madison R, Joyce G, Litwin MS. Increasing costs of urinary incontinence among female Medicare beneficiaries. Urologic Diseases of America Project. J Urol 2006;176:247–51; discussion 251.) As a result, many women with urinary incontinence live with physical, functional, and psychological limitations and diminished quality of life at home and at work. (Harris SS, Link CL, Tennstedt SL, Kusek JW, McKinlay JB. Care seeking and treatment for urinary incontinence in a diverse population. J Urol 2007;177:680–4.)

There are three main types of urinary incontinence—stress urinary incontinence (SUI), urge urinary incontinence (UUI), and mixed incontinence where both SUI and UUI components are

present. SUI is usually associated with symptoms of involuntary loss of urine with activities such as coughing, laughing, sneezing, running, or change in position. SUI is considered an anatomic problem where the lower part of the bladder moves downward with activity or the urethral sphincter has been damaged. Damage to the bladder neck or urethral sphincter is most commonly seen as a long-term complication of childbirth, but can occur in other situations such as menopause, radiation, congenital abnormalities, or surgical trauma. Treatments for SUI aim to treat the anatomic defect and include pelvic floor muscle exercises (Kegels), pessaries to support the bladder neck, and surgery.

UUI is usually associated with symptoms that include frequent urination and the sudden urge to urinate with the loss of urine. UUI is considered a functional or neurologic problem where the bladder muscle (detrusor) contracts inappropriately. Treatments for UUI are directed toward controlling bladder contraction with bladder training, medications, or nerve stimulation therapies. Mixed incontinence is when symptoms or findings of both SUI and UUI are present.

Major risk factors for urinary incontinence include aging, obesity, pregnancy, and smoking (Bump RC, Norton PA Risk factors for stress urinary incontinence. Obstet Gynecol Clin North Am. 1998;25:723–746.) The ability to alter risk factors and reduce the rates of SUI and other pelvic floor disorders has motivated researchers to examine the impact of factors such as aging, pregnancy, route of delivery, ethnic heritage, smoking, obesity, diabetes, and other conditions that may be comorbidities or may affect the development and/or progression of stress incontinence. (Luber, KM. The Definition, Prevalence, and Risk Factors for Stress Urinary Incontinence. Rev Urol. 2004;6: S3–S9.). In 2004. Luber described several key points relevant to this discussion including: 1) Within the next 30 years, the number of women older than 60 years will increase an estimated 82%. This aging of the population has profound implications for those providing health care to women with SUI. 2) The prevalence of both urge and stress incontinence has been shown to increase proportionately to a rising body mass index (BMI). The proportion of persons with a BMI exceeding 30 kg/m^2 increased from approximately 13.4% in 1960 to 30.5% in 2000. This high prevalence of obesity is likely to increase the prevalence of urinary incontinence in the United States. 3) Whether by direct effect or indirectly through smoking-related illnesses that cause increased coughing, such as chronic obstructive pulmonary disease, smoking appears to have a striking causal relationship with SUI.

Unfortunately, the diagnosis of urinary incontinence based on symptoms alone can be misleading. Symptoms related by patients can be inconsistent and/or confusing, so that further information is needed to establish a working diagnosis before initiating even conservative care. Although urodynamics studies are not essential for the routine evaluation of a patient with incontinence, they can be invaluable in assessing patients who present with challenging symptom profiles and are a reasonable prerequisite to surgical intervention. (Luber.)

III. Treatment Options for Stress Urinary Incontinence

Treatment options for SUI include both surgical and non-surgical options. Non-surgical treatments include pelvic floor muscle (Kegel) exercises, vaginal inserts, and pessaries. Patients may opt for the use of conservative measures to treat stress or stress-predominant urinary

incontinence. There are no comparative or direct observational data concerning the use of urethral plugs, continence pessaries, or vaginal inserts in the management of these patients. (AUA/SUFU Guideline: Surgical Treatment of Female SUI, 2017.) Higher incontinence frequency, premenopausal status, lower education level, previous urinary incontinence surgery were found to be risk factors for failure and dissatisfaction with non-surgical therapy for SUI. (Schaffer, J, et al. Predictors of Success and Satisfaction of Nonsurgical Therapy for Stress Urinary Incontinence. Obstet Gynecol. 2012 Jul; 120(1): 91–97.)

Surgical treatments for SUI date back to the late 19th century and dozens of different types of procedures were employed during the 20th century with varying degrees of success, failure, and complications. The first surgical technique that became a routine clinical procedure was developed by Kelly at Johns-Hopkins in 1900. It consisted of anterior colporrhaphy with plication of the tissue surrounding the bladder neck with deep mattress sutures. In 1914, Kelly presented the first detailed analysis and follow up of 20 patients, a milestone in the history of urogynecology that became a standard of care for the next 60 years. (Kelly, HM, Dumm, WM, Urinary Incontinence in Women, without manifest injury to the bladder. Surg Gynec Obstet, 18:444-50, 1914.) In 1949, Marshall, Marchetti, and Krantz developed cystourethropexy and colposuspension, and in 1961 Burch modified this procedure. Almost simultaneously in 1959, Pereyra developed a less invasive needle suspension procedure, and in 1973 Stamey attempted to improve on this using cystoscopic control. (A Brief History of Urinary Incontinence and its treatment. Schultheiss, D., https://www.ics.org/Publications/ICI_3/v1.pdf/historique.pdf.)

Current surgical treatment options for SUI are based on these initial developments in the field and include synthetic mid-urethral slings, autologous fascia pubo-vaginal slings, the Burch colpo-suspension and urethral bulking agents. (AUA/SUFU Guideline: Surgical Treatment of Female SUI, 2017.) The pubovaginal sling insertion procedure involves abdominal and vaginal incisions with placement of a fascial sling at the proximal urethra. The ends of the sling are passed through the tunnels into the retropubic space and are fixed to the anterior rectus fascia providing support to the urethra during increased intra-abdominal pressure. Alternatively, a suspended "sling-on-a-string" method can be used to reduce the invasiveness of the procedure and to shorten the length of sling material required. The Burch procedure involves attaching the periurethral fascia to the iliopectineal ligament with multiple sutures to stabilize the urethra. Surgery can be performed via laparotomy or laparoscopy, and can be robot-assisted. The choice of intervention should be individualized based upon the patient's symptoms, the degree of bother the symptoms cause the patient, patient goals and expectations, and the risks and benefits for a given patient. Although most of these procedures have been available for some time, very little comparative data between these broad treatment categories exists to assist the physician in choosing a therapy.

Autologous fascia pubovaginal slings (PVS) utilize the placement of autologous fascia lata or rectus fascia beneath the urethra to provide urethral supports. These procedures generally require an 8-10 cm abdominal or leg incision to harvest the fascia and vaginal dissection for placement. They have reported success rates between 50% and 75% after follow-up as long as 10 years (Norton P, Brubaker L. Urinary incontinence in women. Lancet. 2006;367(9504):57–67.) Well-controlled and appropriately blinded comparisons of fascial sling versus other anti-incontinence procedures is difficult due to the inherent differences in morbidity of the techniques. The SISTEr

trial compared the fascial sling to the Burch colpo-suspension in a well-conducted RCT. Data suggested effectiveness and need for retreatment favoring the fascial sling over the Burch colpo-suspension (66% versus 49%). This trial used strict composite outcome criteria of no self-reported SUI on questionnaire, no need for retreatment, and a negative stress test. The added morbidity of the fascial harvest should be considered in the preoperative discussion when considering sling type. The separate incisions used to harvest the fascia carry risks of infection, wound complications, and incisional hernia. "Efforts to use other materials, such as porcine dermis and cadaveric fascia, as substitution for the autologous fascia have shown inferior results." (AUA/SUFU Guideline: Surgical Treatment of Female SUI, 2017; Guerrero KL, Emery SJ, Wareham K et al: A randomized controlled trial comparing TVT, Pelvicol and autologous fascial slings for the treatment of stress urinary incontinence in women. BJOG 2010; 117:1493.)

The Burch colpo-suspension is another technique that is generally completed using a large abdominal incision, though it can be completed with a laparoscopic or robot-assisted laparoscopic approach. In examining the Burch procedure in long-term follow up studies up to 20 years, the cure rate appears to decrease with time. Additionally, lower urinary tract symptoms were found to be very common in the long-term with more than three-fourth experiencing these. (Kjølhede, P. Long-term efficacy of Burch colpo-suspension: a 14-year follow-up study. Acta Obstet Gynecol Scand 2005; 84: 767–772., Demirci, F., et al. Long-term results of Burch colpo-suspension. Gynecol Obstet Invest 2001 ;51 :243-247, Alcalay, M. Burch colop-suspension: A 10-20 year follow-up. British Journal of Obstetrics and Gynaecology September 1995, Vol. 102, pp. 740-745.) The colpo-suspension does carry some morbidity with its incision as shown in the SISTEr trial with over 20% of patients having wound-related issues. The SISTEr trial compared the Burch colpo-suspension with the autologous fascial PVS. This comparison had outcome data to five years and favored the autologous fascia PVS over the Burch colpo-suspension due to the lower retreatment rates (4% versus 13%). The data also suggest that the colpo-suspension is likely inferior to fascial sling in most efficacy related outcomes.

Regarding the use of bulking agents, little long-term data exists on their use for the treatment of SUI. Retreatment tends to be the norm for bulking agent therapy, and determination of absolute outcomes accordingly becomes challenging. There is inadequate data to allow the recommendation of one injectable agent over another.

IV. The TVT Mid-Urethral Sling

The TVT device was developed by Professor Ulf Ulmsten and colleagues in Sweden and introduced into clinical practice in 1994-1995. When it was introduced it represented a new concept for the treatment of stress urinary incontinence in women. The TVT procedure involves minimal vaginal dissection, a small vaginal incision at the mid-urethra, and placement of a macroporous, knitted, monofilament Prolene polypropylene tape tension-free at the mid-urethra. The selection of Prolene polypropylene mesh followed trials of other materials that were ultimately rejected due to them causing a prominent inflammatory tissue reaction. After the TVT technique's introduction in Scandinavia, it spread quickly to other parts of the world. (Ulmsten U, An Introduction to Tension-Free Vaginal Tape (TVT) – A New Surgical Procedure for Treatment of Female Urinary Incontinence. Int. Urogynecol J. 2001 (Suppl 2);S3-S4.) The TVT technique was based on the "Integral Theory"—the theory that loose ligaments caused stress urinary incontinence due to inactivation of urethral close forces. (Petros P, Creating a gold

standard surgical device: scientific discoveries leading to TVT and beyond. Int Urogynecol J. 2015 Apr;26(4):471-6; Petros P & Ulmsten U, An Integral Theory and its Method for the Diagnosis and Management of Female Urinary Incontinence. Scand J Urol Nephrol Suppl. 1993;153:1-93.)

The initial reports on the success of the TVT procedure were encouraging. In 1998, Ulmsten reported 12-month follow up on a prospective multi-center study of 131 patients undergoing TVT surgery at six different hospitals in Sweden. The 12-month cure rate was 91% with few intra- or post-operative complications. Complications included one bladder perforation, one vaginal infection, four with short-term urinary retention, and one with a hematoma that resolved without treatment. Patients were discharged from the hospitals within one day and returned to work within two weeks. (Ulmsten, U, et al. A Multicenter Study of Tension-Free Vaginal Tape (TVT) for Surgical Treatment of Stress Urinary Incontinence. lnt Urogynecol J (1998) 9:210-213.) In 2001, Nilsson et al., reported 5-year follow-up results on 90 consecutive patients that underwent the TVT procedure. They reported an overall 87.4% cure rate, with an additional 10% of patients significantly improved and a 4.7% failure rate. No patient complained of long-term voiding difficulties and there were no signs of defective healing or rejection of the tape material. (Nilsson, CG, et al. Long-term Results of the Tension-Free Vaginal Tape (TVT) Procedure for Surgical Treatment of Female Stress Urinary Incontinence. Int Urogynecol J (2001) (Suppl 2):S5 S8.) In 2001, Razepour & Ulmsten reported 4-year follow-up results on 34 patients that underwent the TVT procedure. They reported at overall 82% cure rate, with an additional 9% of patients significantly improved and a 9% failure rate. No patient complained of long-term voiding difficulties and there were no signs of defective healing or rejection of the tape material. (Razepour, M, Ulmsten, U. Tension-Free Vaginal Tape (TVT) in Women with Recurrent Stress Urinary Incontinence – A Long-term Follow up. Int Urogynecol J (2001) (Suppl 2):S9 S11.)

A landmark prospective multicenter randomized controlled trial was published in 2002 demonstrated that TVT procedures were associated with fewer post-operative complications and a shorter recovery period than colposuspension. (Ward K and Hilton P, Prospective multicenter randomised trial of tension-free vaginal tape and colposuspension as primary treatment for stress incontinence. BMJ 2002;325:67.) The authors also published their five-year follow-up results, which showed an 81% cure rate in the TVT group with no significant difference in the colposuspension group. They found that the effect of both procedures on the cure of incontinence and improvement in quality of life was maintained in the long term. (Ward K and Hilton P, Tension-free vaginal tape versus colposuspension for primary urodynamic stress incontinence: 5-year follow up. BJOG. 2008 Jan;115(2):226-33.)

Multiple randomized controlled trials, long-term studies, and systematic reviews and meta-analyses support the safety and efficacy of mid-urethral slings in general—and the TVT in particular—as a surgical treatment of stress urinary incontinence. (Nilsson CG, et al., Seventeen years follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013 Aug; 24(8):1265-9; Serati M, Tension-free Vaginal Tape for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 10-Year Follow-Up. Eur Urol 2012;61:939-946; Aigmueller T, et al., Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol 2011 Nov;205(5):496.e1-5; Olsson I, et al., Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary

incontinence: a retrospective follow-up 11.5 years post-operatively. Int Urogynecol J 2010 Jun;21(6):679–683; Liapis A, et al., Long-term efficacy of tension-free vaginal tape in the management of stress urinary incontinence in women: efficacy at 5- and 7-year follow-up. Int Urogynecol J 2008 Nov;19(11):1509-1512; Laurikainen E, et al., Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol 2014 Jun;65(6):1109–14; Chêne G, et al., Long-term results of tension-free vaginal tape (TVT) for the treatment of female urinary stress incontinence. Eur J Obstet Gynecol Reprod Biol 2007 Sep;134(1):87-94; Serati M, et al., TVT for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 13-Year Follow-Up. Neurourol and Urodynamics DOI 10.1002/nau; Song PH, et al., The 7-year outcome of the tension-free vaginal tape procedure for treating female stress urinary incontinence. BJU Int 2009 Oct;104(8):1113-1117; Jelovsek JE, et al, Randomized trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow up. BJOG 2008 Jan;115(2):219-225; Svenningsen R, et al., Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013 Aug;24(8):1271-8; McCracken GR, et al., Five Year Follow-up Comparing Tension-Free Vaginal Tape and Colposuspension, Ulster Med J 2007 Sep;76(3):146-149; Heinonen P, et al., Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. Int J Urol. 2012 Nov;19(11):1003-9; Vesna Bjelic-Radisic V, Patient-related Outcomes and Urinary Continence Five Years After the Tension-Free Vaginal Tape Operation, Neurourology and Urodynamics 2011;30(8):1512-1517; Prien-Larsen JC, et al., Long-term outcomes of TVT and IVS operations for treatment of female stress urinary incontinence: monofilament vs. multifilament polypropylene tape. Int Urogynecol J 2009 Jun;20(6):703-709; Jin-Yan Wu JY, et al., Surgical therapies of female stress urinary incontinence: experience in 228 cases, Int Urogynecol J 2010 Jun;21(6):645-649; Celebi I, et al., Results of the tension-free vaginal tape procedure for treatment of female stress urinary incontinence: a 5 year follow-up. Arch Gynecol Obstet 2009 Apr;279(4):463-467.)

Long-term studies

Focusing more closely on long-term studies, in 2009, Olsson and colleagues published follow-up 10-13 years after TVT surgery and reported long-term continence rates remained high (77-84%), while 94% of patients were still satisfied with their results and no late mesh exposures were noted. This compares favorably with long-term follow-up from Burch colpopexy where continence rates declined significantly in the long term to 63% at 6-years (Kjølhede P (2005) Long-term efficacy of Burch colposuspension: a 14-year follow-up study. Acta Obstet Gynecol Scand 84:767–772; Olsson, I, Abrahamsson, AK, Kroon, UB. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence - A retrospective follow-up 11.5 years post-operatively. Int Urogynecol J (2010) 21:679–683.)

In 2011, Groutz reported on 52 patients who underwent TVT surgery in 2000. Preoperatively, while all patients reported substantial SUI, and 28 (54%) also had concomitant UUI. At 10 years postoperatively, 34 women (65%) considered their condition cured, 6 (12%) believed it was improved, and 12 (23%) thought surgery had failed. Eleven women (21%) reported SUI, 22 (42%) had UUI (de novo UUI in 9), and 8 (15%) had recurrent urinary tract infections. Two women (4%) underwent repeated TVT. (Groutz A, et al. Ten-Year Subjective Outcome Results

of the Retropubic Tension-Free Vaginal Tape for Treatment of Stress Urinary Incontinence. J Minim Invas Surg, 18, 726–729, 2011.)

In 2012, Heinonen reported on the 10.5-year follow-up on 138 patients who had undergone the TVT procedure from 1998-2000. The group included both patients with SUI and mixed urinary incontinence. Continence rates continued in the long term at 78-90%. However, the group with mixed incontinence initially had initial and long-term lower cure rates than patients with pure SUI. Only 3 of 138 patients evaluated had late-term complications, two with urinary retention and one with tape erosion in the bladder and recurrent urinary tract infections. The TVT tape was cut below the urethra in two patients; one because of urinary retention at 1 year after the operation and another because of pain at 8 years. The symptoms of both patients disappeared after the re-intervention and the patients remained stress continent. Hospital records of the original cohort did not show any additional complications. (Heinonen, P, Ala-Nissilä, S, Kiilholma, P, Laurikainen, E. Tension-free vaginal tape procedure without preoperative urodynamic examination: Long-term outcome. Int J Urol (2012) 19, 1003–1009.)

In 2013, Svenningsen reported on follow-up of > 10-years in 483 patients who underwent the TVT procedure. Continence was maintained after 10 years in 76-90 % of patients with 83% stating they were "very happy" with the surgery. Subjective voiding difficulties were reported by 22.8%, the most common being a slow stream or intermittency. However, the "very satisfied" rates were almost identical among those with and without subjective voiding problems and there were no differences in objectively low urinary flow between the groups. They therefore considered it unlikely that the reported voiding difficulty represented a serious clinical problem. The total number of mesh exposures for the whole 10-year period was 4 (0.8%). (Svenningsen, R, Staff, AC, Schiøtz, HA, Western, K, Kulseng-Hanssen, KS. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J (2013) 24:1271–1278.)

In 2012, Serati and colleagues reported on the 10-year follow-up of 63 patients who underwent the TVT procedure. They reported cure rates of 90-93%. Intraoperatively, bladder perforation occurred in two cases; no severe bleeding or other complications occurred. At 3 months after surgery, the presence of de novo overactive bladder (OAB) symptoms was 30%, but this decreased with time to 19% despite the aging of patients. (Serati, M. et al. Tension-free Vaginal Tape for the Treatment of Urodynamic Stress Incontinence: Efficacy and Adverse Effects at 10-Year Follow-Up. Europ Urol 61;939-46, 2012.)

In 2008 & again in 2013, Nilsson reported on a cohort of 90 women operated upon with the TVT procedure at three Nordic centers prospectively followed for 17 years. Over 90 % of the women were objectively continent. 87% percent were subjectively cured or significantly improved. One case of a minimal, symptom-free tape exposure was seen. No other tape complications occurred. An important observation is that there seemed to be no shrinkage of the TVT mesh over time, as suggested by PVR volumes within normal ranges, except for 2 patients with concomitant diseases. (Nilsson, CG, Palva, K, Aarnio, R., Morcos, E, Falconer C. Eleven years prospective follow-up of the tension-free vaginal tape procedure for treatment of stress urinary incontinence. Int Urogynecol J (2008) 19:1043–1047; Nilsson, CG, Palva, K, Aarnio, R., Morcos, E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013 Aug;24(8):1265-9.)

In 2017, Song reported on 226 women who underwent the TVT procedure. At 13 years after surgery, the overall cure rate was 82.5%, with a satisfaction rate of 67.5%. Twenty-one patients (10.2%) had postoperative complications at 1-year follow-up after surgery. However, at 13 years follow-up after surgery, only three patients (1.5%) had any further postoperative complications, including mesh exposure in one patient and de novo urgency in two patients. (Song PH, Kwon DH, Ko YH, Jung HC. The Long-Term Outcomes of the Tension-free Vaginal Tape Procedure for Treatment of Female Stress Urinary Incontinence: Data from Minimum 13 Years of Follow-Up. Low Urin Tract Symptoms. 2017 Jan;9(1):10-14.)

Another 10-year follow up study of 141 patients demonstrated the TVT procedure had a 57-84% cure rate. Three patients experienced mesh exposure during the follow-up period. Eleven of 141 patients (7.8%) had been re-operated on for incontinence or reasons related to the TVT procedure: 4 patients underwent further anti-incontinence procedures. Six procedures were performed to relieve voiding obstruction including 1 urethrotomy (120 months after surgery), followed by urethral mesh erosion. In 1 patient transurethral removal of bladder stones (30 and 42 months after TVT) and resection of mesh eroded into the bladder per laparotomy (50 months after TVT) was necessary. (Aigmueller T, Trutnovsky G, Tamussino K, et al. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol 205(5);496.e1–496.e, 2011.)

In Aigmueller's study, 54 of 141 patients (38%) reported having urinary urgency symptoms preoperatively. Thirty-four of these 54 (63%) were free of OAB symptoms at follow-up. Conversely, 17 of 83 (20%) patients without urgency preoperatively reported urgency at 10 years. In 17% of patients (20/117), detrusor over-activity was seen during cystometry. Ten of these 20 women had OAB symptoms; the other 10 patients were asymptomatic regarding OAB symptoms. In large epidemiologic studies, the prevalence of OAB symptoms in postmenopausal women, according to the International Continence Society definition, varies between 20% and 40%, increasing with age. The authors concluded that the prevalence of OAB symptoms was consistent with the prevalence in their study population at the time of follow-up. Thus, they concluded that TVT does not appear to raise the risk for OAB symptoms significantly. At 10-year follow-up, the clinical stress test was negative in 84%, slightly positive in 8.5%, and strongly positive in only 4.3%. 57% of the patients considered themselves cured, 23% improved, 6.4% unchanged, and 11% worse. (Aigmueller T, Trutnovsky G, Tamussino K, et al., Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011 Nov;205(5):496.e1-5.)

From a slightly different perspective, long-term 5-year data comparing the TVT with the transobturator sling (TOT) was published in 2015. The authors extended their follow up of patients in the original 2-year study. They found both the TVT and TOT groups had a slight decline in continence during years 3-5 in the study, but satisfaction rates remained high in both groups. Mesh exposures were also noted to continue to occur in years 3-5, but the overall rate of mesh exposure in both groups remained low at <2%. (Kenton, K, et al. 5-Year Longitudinal Follow-up after Retropubic and Transobturator Midurethral Slings. J Urol. 2015 January; 193(1): 203–210.)

Another report comparing TVT with TOT from 2010 was a 5-year prospective randomized clinical trial of 72 patients comparing where the overall cure rate at 5-years was 72% and no differences between the groups was observed. Three mesh exposures were noted—2 in the TVT group and 1 in the TOT group. The most prevalent complications observed at 5-year follow-up were de novo urgency symptoms (5%), dyspareunia (3.3%), and incontinence during intercourse (6.6%). The incidence of overactive bladder symptoms such as de novo urgency and frequency, as previously reported, appeared to increase in each group within the first month after surgery and to decrease at 5 years. (Angioli, R, et al. Tension-Free Vaginal Tape Versus Transobturator Suburethral Tape: Five-Year Follow-up Results of a Prospective, Randomised Trial. Eur Urol 58: 671-677, 2010.) Another study of 273 patients demonstrated a 5-year objective cure rate was 84.7% in the TVT group and 86.2% in the TVT-O group, with no statistical difference between the groups. Subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, with no difference between groups. Complication rates were low, with no difference between groups. (Laurikainen, E, et al. Five-year Results of a Randomized Trial Comparing Retropubic and Transobturator Midurethral Slings for Stress Incontinence. Eur Urol. 2014 Jun;65(6):1109-14.)

Systematic reviews and meta-analyses

Focusing on systematic reviews and meta-analyses, several publications can be found that support the safety and efficacy of mid-urethral slings. Ford published a Cochrane Review in 2015 and 2017 on mid-urethral sling operations for stress urinary incontinence in women (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database of Systematic Reviews 2015, Issue 7, Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database of Systematic Reviews 2017.) They included 81 trials that evaluated 12,113 women. Fifty-five trials with data contributed by 8,652 women compared the use of the TVT sling type with TOT sling type. They found moderate quality evidence that in the short term (up to one year) the rate of subjective cure of TVT and TOT are similar (36 trials, 5514 women; moderate quality evidence) ranging from 62% to 98% in the TOT group, and from 71% to 97% in the TVT group. Fewer trials reported medium-term (one to five years) and longer-term (over five years) data, but subjective cure was again similar between the groups (5 trials, 683 women; low quality evidence; and 4 trials, 714 women; moderate quality evidence, respectively). In the long term, subjective cure rates ranged from 43% to 92% in the TOT group, and from 51% to 88% in the TVT group.

MUS procedures performed using the TVT had higher morbidity when compared to TOT, though the overall rate of adverse events remained low. The rate of bladder perforation was lower after TOT (0.6% versus 4.5%; 40 trials, 6372 women; moderate quality evidence). Major vascular/visceral injury, mean operating time, operative blood loss and length of hospital stay were lower with TOT.

Postoperative voiding dysfunction was less frequent following TOT (37 trials, 6,200 women; moderate quality evidence). Overall rates of groin pain were higher in the TOT group (6.4% versus 1.3%; 18 trials, 3,221 women; moderate quality evidence) whereas suprapubic pain was

lower in the TOT group (0.8% versus 2.9%;); both being of short duration. The overall rate of vaginal tape erosion/exposure/extrusion was low in both groups: 24/1,000 instances with TOT compared with 21/1,000 for TVT (31 trials, 4,743 women; moderate quality evidence). There were only limited data to inform the need for repeat incontinence surgery in the long term, but it was more likely in the TOT group than in the TVT group (4 trials, 695 women; low quality evidence). At 2-year follow-up, rates of superficial and deep dyspareunia were noted to be low, with no difference between the TVT and TOT groups. In the 10 trials addressing sexual function, there was significant improvement in sexual function from baseline scores during the follow up period spanning 6-24 months.

The authors concluded that "[m]mid-urethral sling operations have been the most extensively researched surgical treatment for SUI in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI."

Schimpf and Colleagues presented a systematic review and meta-analysis of randomized controlled trials from 1990-2013 with a minimum 12 months of follow-up comparing sling procedures for SUI to another sling or Burch urethropexy. (Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014.) For midurethral slings (MUS) vs Burch, meta-analysis of objective cure showed no significant difference. Therefore, they suggested either intervention, and noted that the decision should balance potential adverse events (AEs) and concomitant surgeries. For women considering pubo-vaginal sling vs Burch, the evidence favored pubo-vaginal slings for both subjective and objective cure. They recommended pubo-vaginal sling to maximize cure outcomes. For pubo-vaginal slings vs MUS, meta-analysis of subjective cure favored MUS. For obturator slings vs retropubic MUS, meta-analyses for both objective and subjective cure favored retropubic slings but were not significant. Meta-analysis of satisfaction outcomes favored obturator slings but was not significant. The authors noted that adverse events were variable between slings; meta-analysis showed overactive bladder symptoms were more common following retropubic slings. The authors recommended either retropubic or obturator slings for cure outcomes, noting that the decision should balance adverse events.

Tommaselli reported on the 3-5 year follow-up of patients who had TVT or TOT slings procedures (Tommaselli GA, Di Carlo C, Formisano C, Fabozzi A, Nappi C. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and meta-analysis. Int Urogynecol J. 2015 Sep;26(9):1253-68.) Data from 49 studies were included. Patients undergoing TVT had similar objective cure rates but higher subjective cure rates than those who had a TOT procedure. Bladder injuries were more frequent and vaginal erosions were less frequent for TVT. Pain-related complications were more common with TO-MUS than with minimally invasive tapes. The authors concluded that MUS have similar objective cure rates in the long term and medium term, and that TOT is associated with a lower subjective cure rate than TVT.

In 2013, Cox and colleagues published a review on the surgical management of SUI. (Cox, A. et al. Surgical management of female SUI: is there a gold standard? Nat. Rev. Urol 10: 78–89, 2013.) In it, they discussed that, "The traditional gold standards of Burch retropubic colposuspension and pubo-vaginal slings are still appropriate treatment options for some patients, but randomized controlled trials have demonstrated that synthetic midurethral slings are just as effective as these traditional procedures but with less associated morbidity. Thus, midurethral slings—inserted via a retro-pubic or transobturator approach—have become the new gold standard first-line surgical treatment for women with uncomplicated SUI." They also noted that "[r]etropubic midurethral slings are associated with slightly higher success rates than transobturator slings, but at the cost of more postoperative complications. Pubo-vaginal slings remain an effective option for women with SUI who have failed other procedures, have had mesh complications, or who require concomitant urethral surgery. Single-incision slings have a number of benefits, including decreased operative times and early return to regular activities, but they are yet to be shown to be as effective as midurethral slings. Both retropubic and transobturator midurethral slings are effective for patients with mixed urinary incontinence, but the overall cure rate is lower than for patients with pure SUI. Based on the literature a new gold standard first-line surgical treatment for women with SUI is the synthetic midurethral sling inserted through a retropubic or transobturator approach."

Fusco and colleagues published a systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in 2018. They identified 28 RCTs, and their meta-analysis included 15,855 patients. They found that patients who received MUS had significantly higher overall and objective cure rates than patients who had Burch procedures. Patients who had MUS and pubovaginal slings had similar cure rates. Patients who received retropubic MUS like the TVT had higher subjective and objective cure rates than the patients who received trans-obturator MUS, but the trans-obturator sling patients had a lower risk of intra-operative bladder or vaginal perforation, pelvic hematoma, UTI, and voiding lower urinary tract symptoms. The authors concluded that their analysis confirmed the superiority of MUS over Burch colposuspension, and that the studies comparing retropubic and trans-obturator MUS showed higher subjective and objective cure rates for the retropubic slings, but with higher risks of some complications and voiding lower urinary tract symptoms. (Fusco F, Abdel-Fattah M, Chapple CR, et al., Updated Systematic Review and Meta-analysis of the Comparative Data on Colposuspensions, Pubovaginal slings, and Midurethral tapes in the Surgical Treatment of Female Stress Urinary Incontinence. Eur Urol. 2017 Oct;72(4):567-91.)

Most recently, Imamura and colleagues reviewed and analyzed 175 randomised controlled trials including 21,598 women. (Imamura, M, et al. Surgical interventions for women with stress urinary incontinence: systematic review and network meta-analysis of randomized controlled trials. BMJ 2019;365:l1842, 2019.) Results showed that the interventions with highest cure rates were traditional sling, retropubic midurethral sling (MUS), open colposuspension, and transobturator MUS, with rankings of 89.4%, 89.1%, 76.7%, and 64.1%, respectively. The authors noted that, compared with retropubic MUS, the odds ratio of cure for traditional sling was 1.06 (95% credible interval 0.62 to 1.85), for open colposuspension was 0.85 (0.54 to 1.33), and for trans-obturator MUS was 0.74 (0.59 to 0.92). Women were also more likely to experience an improvement in their incontinence symptoms after receiving retropubic MUS or trans-obturator MUS compared with other surgical procedures. In particular, compared with

retropubic MUS, the odds ratio of improvement for trans-obturator MUS was 0.76 (95% credible interval 0.59 to 0.98), for traditional sling was 0.69 (0.39 to 1.26), and for open colposuspension was 0.65 (0.41 to 1.02). The quality of evidence was moderate for retropubic MUS versus transobturator MUS and low or very low for retropubic MUS versus the other two interventions. Data on adverse events were available mainly for mesh procedures, indicating a higher rate of repeat surgery and groin pain, but a lower rate of suprapubic pain, vascular complications, bladder or urethral perforation, and voiding difficulties after trans-obturator MUS compared with retropubic MUS. Data on adverse events for non-MUS procedures were sparse and showed wide confidence intervals. Long-term data were limited. They concluded that the retropubic MUS, trans-obturator MUS, traditional sling, and open colposuspension are more effective than other procedures for stress urinary incontinence in the short to medium term. Data on long-term effectiveness and adverse events are, however, limited, especially around the comparative adverse events profiles of MUS and non-MUS procedures.

Large population-based studies

The use of mid-urethral slings have also been reported in large population-based studies. In 2015, Welk reported a 10-year retrospective study on complications of mesh sling surgeries. (Welk B, Al-Hothi H, Winick-Ng J. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015 Dec;150(12):1167-75. doi: 10.1001/jamasurg.2015.2590.) Of 59,887 Canadian women who underwent a mesh-based procedure, 1307 women (2.2%) underwent a mesh revision, removal or other treatment of other complication. The authors concluded that the intervention rates for mesh-based complications in procedures for SUI were similar to those seen in the reports from other countries and that complications related to the placement of mesh slings for the treatment of SUI appear to be lower than those associated with procedures for pelvic organ prolapse.

In 2013, Jonsson Funk reported on the long-term risk of sling revision/removal in population of over 44 million women. (Jonsson Funk M, Siddiqui NY, Pate V, et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol 208: 73.e1-7, 2013.) In this study, the authors identified 188,454 women who underwent a mesh sling procedure. The 9-year cumulative risk of sling revision/removal was relatively low at 3.7% with 60% of revisions/removals caused by mesh exposures and the majority of revision/removals occurring within the first few years after the index surgery.

In 2016, Unger reported on 3,307 women who underwent sling placement. (Unger CA, Rizzo AE, Ridgeway B. Indications and risk factors for midurethral sling revision. Int Urogynecol J. 2016 Jan;27(1):117-22.) From this cohort, the overall rate of revision surgery was only 2.7 %. Of the 89 revision procedures, the indications included: urinary retention (43.8%), voiding dysfunction (42.7%), recurrent urinary tract infection (20.2%), mesh erosion (21.3%), vaginal pain/dyspareunia (7.9%), and groin pain (3.4%). Urinary retention and voiding dysfunction were the most common indications. Patients with a history of previous SUI surgery and concomitant apical suspension at the time of sling placement may be at higher risk of requiring revision surgery.

In 2012, Nguyen reported on the perioperative complication and reoperation rates associated with slings and prolapse repairs using mesh and biologic grafts in the population of women who underwent sling procedures or pelvic organ prolapse surgeries using implanted grafts or mesh between from 2008, to 2010 in the Kaiser Permanente system in California and Hawaii. (Nguyen JN, Jakus-Waldman SM, Walter AJ, White T, Menefee SA. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol. 2012 Mar;119(3):539-46.) They identified 3,747 women who underwent slings and using implanted prostheses. Trocar-related bladder perforations occurred in 51 (1.4%) and urethral perforations occurred in 2 (0.05%)of patients. Mesh-related reoperations after sling procedures were performed for voiding dysfunction or urinary retention in 49 (1.3%), vaginal mesh erosion in 30 (0.8%), and urethral erosion in 3 (0.08%).

Professional Society Statements

Multiple professional societies and organizations have voiced their support for polypropylene mesh mid-urethral slings like the TVT device. The American Urogynecologic Society and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction issued a position statement on mesh mid urethral slings for stress urinary incontinence in 2014, which has been twice updated. (Published January 2014; Updated June 2016; Updated February 2018. https://www.augs.org/assets/1/6/AUGS-SUFU_MUS_Position_Statement.pdf). The statement included the following points, with which I agree: 1) Polypropylene material is safe and effective as a surgical implant. 2) The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history. 3) Polypropylene mesh midurethral slings are a standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for patients. 4) The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of stress urinary incontinence.

The AUGS/SUFU statement concludes, “The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.” The position statement is also supported by the following organizations: The American Association of Gynecological Laparoscopists, The American College of Obstetricians and Gynecologists, The National Association for Continence, the International Urogynecological Association, and the Society of Gynecologic Surgeons.

In November 2015, ACOG/ AUGS updated a Practice Bulletin on the Management of Urinary incontinence (#144, November 2015.) It contains the following statements with which I also agree: “Initial midurethral sling surgery results in higher 1-year subjective and objective cure rates than pelvic floor physical therapy in women with stress urinary incontinence. Synthetic

midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colpo-suspension, and laparoscopic colpo-suspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colpo-suspension than with synthetic midurethral slings. There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women."

In 2015, The AUA published a position statement on the use of vaginal mesh for the surgical treatment of SUI (https://www.auanet.org/guidelines/use-of-vaginal-mesh-for-the-surgical-treatment-of-stress-urinary-incontinence). It contained the following important statements, again with which I agree, "Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of follow-up. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional non-mesh sling techniques. The AUA Guideline also indicates that intra-operative cystoscopy should be performed during all synthetic sling procedures to identify urinary tract injury."

In order to better understand the use of surgical mesh slings for SUI and evaluate their safety and effectiveness, In September 2011, the FDA held a panel meeting of scientific experts. and conducted a systematic review of the published scientific literature from 1996 to 2011 (Obstetrics and Gynecology Devices Panel of the Medical Device Advisory Committee, https://www.fda.gov/medical-devices/urogynecologic-surgical-mesh-implants/considerations-about-surgical-mesh-sui.) For surgical mesh slings used for SUI, both the panel and the FDA's review found that, 1) The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year. Longer follow-up data is available in the literature, but there are fewer of these long-term studies compared to studies with one-year follow-up. 2) Mesh sling surgeries for SUI have been reported to be successful in approximately 70 to 80 percent of women at one year, based on women's reports and physical exams. Similar effectiveness outcomes are reported following non-mesh SUI surgeries. 3) The use of mesh slings in transvaginal SUI repair introduces a risk not present in traditional non-mesh surgery for SUI repair, which is mesh erosion, also known as extrusion. 4) Erosion of mesh slings through the vagina is the most commonly reported mesh-specific complication from SUI surgeries with mesh. The average reported rate of mesh erosion at one year following SUI surgery with mesh is approximately 2 percent. Mesh erosion is sometimes treated successfully with vaginal cream or an office procedure where the exposed piece of mesh is cut. In some cases of mesh erosion, it

may be necessary to return to the operating room to remove part or all of the mesh. 5) The long-term complications of surgical mesh sling repair for SUI that are reported in the literature are consistent with the adverse events reported to the FDA. 6) The complications associated with the use of surgical mesh slings currently on the market for SUI repair are not linked to a single brand of mesh.

The design of the TVT device has many positive attributes that have made it the gold standard treatment for stress urinary incontinence. It is macroporous, lightweight mesh that is known for its excellent biocompatibility. The large pore size results in excellent tissue integration into the mesh and low infection rates. It is implanted in a minimally invasive procedure that typically does not require a hospital stay, and allows for a faster return to the patient's regular activities than alternative surgical procedures. It is implanted through a very small vaginal incision and two small suprapubic incisions, and the small incision size reduces the risk of wound complications such as infection or dehiscence. The fact that the device is made from Prolene polypropylene is comforting for surgeons, as the integrity and biocompatibility of the material is well-known. The fact that the sling is implanted via a small incision at the mid-urethra is a positive design attribute, as the mid-urethra is just inside the vaginal introitus and therefore readily accessible to the surgeon. The surgery can be performed under local anesthesia, which reduces the anesthesia risks to the patient and makes the procedure available to patients who may not be able to tolerate general anesthesia well. The fact that the device comes sterilized, with instructions for use, and with an extensive history of data supporting it also is helpful to the surgeon. The fact that the sling is placed in a tension-free manner is a positive design attribute because it reduces the likelihood of post-operative urinary retention from over-tightening of sutures (such as in a Burch procedure) or fascial slings.

This published data from long-term studies, systematic reviews and meta-analyses, as well as large population-based studies and resulting professional society recommendations demonstrates that the TVT is a safe and effective device that is minimally invasive and allows an earlier return to activities than alternative procedures. Its benefits outweigh its risks, and it is not defectively designed.

V. Potential Complications

a. Pain

Pelvic pain is not an uncommon condition; reported to be present in 39% of women. (Jamieson DJ and Steege JF, The Prevalence of Dysmenorrhea, Dyspareunia, Pelvic Pain, and Irritable Bowel Syndrome in Primary Care Practices. Obstet Gynecol. 1996 Jan;87(1):55-58; Glatt AE, et al., The Prevalence of Dyspareunia. Obstet Gynecol. 1990 Mar;75(3):433-36.) The rates of pain and dyspareunia with MUS, however, are very low. (Richter, H.E., et al., Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med, 2010. 362(22): p. 2066-76.) The SGS systematic review and meta-analysis notes that there is a 0% incidence of dyspareunia with retropubic MUS like the TVT. (Schimpf 2014.) The 2015 and 2017 Cochrane Review re MUS notes that the reported occurrence of problems with intercourse including pain following MUS surgery was low, and sexual function was noted to significantly improve following MUS surgery. Rates of superficial and deep dyspareunia following MUS surgery were

low. (Ford 2015 & 2017.) In a systematic review and meta-analysis published in 2015, Tommaselli and colleagues noted that the rate of persistent or chronic pain following retropubic MUS surgery of 0.3% (13 out of 3,974). (Tommaselli GA, et al., Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015;26:1253-68.) MUS revision surgery for vaginal pain/dyspareunia is rare; reportedly occurring in approximately 0.2% of patients. (Unger 2016.)

Systematic reviews and meta-analyses show that trans-obturator mid-urethral slings are associated with more pain compared to retropubic slings like the TVT. (Tommaselli GA, et al., Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015;26:1253-68; Schimpf 2014.) Pelvic pain, vaginal pain, and dyspareunia are risks of every surgical treatment of stress urinary incontinence. When pelvic pain, vaginal pain, or dyspareunia occur following a TVT surgery, it is not the result of an alleged defect in the TVT device or any inherent characteristic of the device.

b. Erosion or Exposure

Mesh erosions or exposures are not attributable to an alleged defect in the TVT or any inherent characteristic in the TVT device. Mesh exposures or erosions are well-known complications of sub-urethral sling placement. The fact that a mesh exposure occurs is not indicative of any defect in the product. The IFU for the TVT warns the surgeon of the risk of erosion or extrusion. In 2008, the FDA issued a Public Health Notification, warning of erosion. But the published literature on mesh exposures shows that they happen very infrequently. (Ford 2015 & 2017 (2.09% overall erosion rate for MUS); Schimpf 2014 (1.4% exposure rate with RP MUS); Fusco F, et al., Updated Systematic Review and Meta-analysis of the Comparative Data on Colposuspensions, Pubovaginal Slings, and Midurethral Tapes in the Surgical Treatment of Female Stress Urinary Incontinence. Eur Urol 2017;72:567-91 (noting a 1.8% vaginal erosion rate with RP MUS.) Large-population-based cohort studies have reported the incidence of re-operation due to mesh erosion to be very low. (Jonsson Funk M, et al, Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol 2013;208:73.e1-7 (noting a 2.5% 9-year risk of revision/removal due to mesh erosion); Unger 2016 (noting a revision rate for mesh erosion of 0.5%).) The Type 1 mesh in the TVT device has the highest biocompatibility of any type of mesh. (Ford Cochrane Review 2015 & 2017.) Patient factors such as vaginal atrophy, diabetes, and smoking can contribute to mesh exposures or erosions, as can technique-related factors such as superficial dissection during mesh placement. (Kokonali MK, et al., Risk factors for mesh erosion after vaginal sling procedures for urinary incontinence. Eur J Obstet & Gynecol and Reprod Biol. 2014;177:146-50.) Wound dehiscence following mid-urethral sling surgery can be termed a mesh exposure, but wound dehiscence can occur following any surgery, regardless of whether mesh is used.

c. Urinary Problems

Recurrent incontinence is not caused by any alleged defect in the TVT or any inherent characteristic of the TVT device. No surgical procedure is 100% effective; recurrent

incontinence is a possibility with any stress incontinence surgery. Persistent or recurrent SUI following any SUI surgery is not uncommon. (Kobashi KC, et al., Surgical Treatment of Female Stress Urinary Incontinence: AUA/SUFU Guideline. J Urol. 2017 Oct;198(4):875-883.) But mid-urethral slings like the TVT have been extensively studied and have been shown to have excellent efficacy. The authors of a 2015 and 2017 Cochrane review noted that "Mid-urethral sling operations have been the most extensively researched surgical treatment for stress urinary incontinence (SUI) in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term." (Ford AA, et al., Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;(7):CD006375.)

Any surgical procedure for the treatment of incontinence can cause new-onset overactive bladder symptoms. (Kobashi 2017; Schimpf 2014.) Overactive bladder symptoms such as urinary urgency and frequency, in their more severe form, can progress to what is known as urge urinary incontinence. The mechanism of urge urinary incontinence is separate from that of stress urinary incontinence. Stress urinary incontinence is primarily an anatomic problem which can be corrected with "Kegel" exercises, pessaries, or surgery. Urge urinary incontinence is more of a functional bladder muscle/nerve problem and is treated with "timed-voiding", medications or nerve stimulation therapy.

VI. Response to Plaintiffs' Experts' Contentions

The mesh in the TVT device is a Type I mesh made of Prolene polypropylene. It is a lightweight (100 g/m^2) macroporous (1,379 µm) mesh. (Moalli PA, et al., Tensile properties of five commonly used mid-urethral slings relative to the TVT^{TM}, Int Urogynecol J. 2008;19:655-63.) Type I mesh like that in the TVT device has been noted to have "the highest biocompatibility with the least propensity for infection." (Ford 2015 & 2017.) Macroporous meshes (pore size > 75 µm) like the TVT have been noted to "easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection." (Ford 2015 & 2017.) Dr. Ulmsten and colleagues—the inventors of the TVT device—selected Prolene mesh as the ideal material for the device after trying other types of materials such as Gore-Tex and Mersilene and finding they did not perform as well as Prolene mesh. (Ulmsten U, et al., An Ambulatory Surgical Procedure Under Local Anesthesia for Treatment of Female Urinary Incontinence. Int Urogynecol J. 1996;7:81-86; Petros P, Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond. Int Urogynecol J 2014.)

I have not seen—nor does the high-quality published literature support—degradation of the Prolene polypropylene, shrinkage, inadequate pore size, excessive weight, chronic problematic foreign body reaction, cytotoxicity, cancer, fraying, roping, or particle loss with TVT slings. It shows that the purported microscopic degradation some have claimed to witness with polypropylene slings is actually a coating of cracked biologic material that can be removed to reveal pristine polypropylene underneath. (de Tayrac R and Letouzey V, Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery. Int Urogynecol J 2011 Jul;22(7):775-80; Thames SF, et al., The myth: in vivo degradation of polypropylene-based

meshes. Int Urogynecol J 2017 Feb;28(2):285-97.) The published studies and my own experience with polypropylene mesh mid-urethral slings including the TVT demonstrate that the material does not degrade; the slings are effective in the long-term and very well-tolerated by the body.

The literature also documents that the slings do not undergo clinically significant shrinkage or migration. (Lo T-S, et al., Ultrasound Assessment of Mid-Urethra Tape at Three-Year Follow-Up After Tension-Free Vaginal Tape Procedure. J Urol. 2004;63(4):671-75; Dietz HP, et al., Does the tension-free vaginal tape stay where you put it? Am J Obstet Gynecol. 2003 Apr;188(4):950-53; Nilsson CG, et al.., Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J 2013; Lukacz ES, et al., The effects of the tension-free vaginal tape on proximal urethral position: a prospective, longitudinal evaluation. Int Urogynecol J 2003;14:179-84.)

While some experts for plaintiffs in pelvic mesh litigation have suggested an association between cancer and polypropylene mesh implantation, the published literature shows there is no basis to believe that the polypropylene in mid-urethral slings like the TVT is associated with cancer. (Moalli P, et al., Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. 2014;25:573-76; Linder BJ, et al., Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. Int Urogynecol J. 2016 Sep;27(9):1333-6; King AB and Goldman HB, Current Controversies Regarding Oncologic Risk Associated with Polypropylene Midurethral Slings. Curr Urol Rep. 2014;15:453.)

The published literature shows no difference in clinical performance between mechanically cut meshes and laser-cut meshes, and Ethicon's internal testing of laser-cut and mechanically cut meshes indicated that the physical properties that might affect clinical performance of the two types of mesh were essentially the same. (4/18/06 Clinical Expert Report, ETH.MESH.00167104-10.) Rusavy and colleagues reported that there was no clinically significant difference between mechanically cut and laser-cut TVT-O slings. (Rusavy Z, et al., Are the same tapes really the same? Ultrasound study of laser-cut and mechanically cut TVT-O post-operative behavior. Int Urogynecol J. 2018 Sep;29(9):1335-1340.)

I am unaware of larger pore or lighter-weight meshes with the proven track record that the TVT mesh has. One study involving the treatment of SUI with larger-pore, lighter weight meshes showed that the use of those meshes did not avoid the risks of vaginal erosion, urethral erosion, urine retention, recurrent incontinence, or de novo urgency. (Okulu E, et al., Use of three types of synthetic mesh material in sling surgery: A prospective randomized clinical trial evaluating effectiveness and complications. Scan J Urol. 2013 Jun;47(3):217-24.) Furthermore, autologous fascial sling procedures present risks not present with the TVT procedure. They require a separate surgical site used to harvest the autologous fascia. Allograft slings have higher failure rates and can undergo resorption. (Soergel TM, et al., Poor Surgical Outcomes after Fascia Lata Allograft Slings. Int Urogynecol J 2001;12:247-53; Carbone JM, et al., Pubovaginal Sling Using Cadaveric Fascia and Bone Anchors: Disappointing Early Results. J Urol. 2001 May;165:1605-11; Fitzgerald MP, et al., Medium-term follow-up on use of freeze-dried, irradiated donor fascia for sacrocolpopexy and sling procedures. Int Urogynecol J 2004;15:238-42; Huang YH, et al.,

High Failure Rate Using Allograft Fascia Lata in Pubovaginal Sling Surgery for Female Stress Urinary Incontinence. J Urol 2001;58(6):943-6.)

Some experts for plaintiffs in pelvic mesh litigation have also suggested that procedures such as the Burch colposuspension are safer than synthetic slings because "life-altering long-term complications do not occur with Burch like they do with synthetic slings, including chronic debilitating pain, chronic sexual dysfunction and dyspareunia". Statements like these have been made without any supporting data and are simply not true. Published data actually shows just the opposite. For instance, in 2001, Demerci reported that approximately 10% of 220 women who underwent a Burch procedure and were followed for an average of 4.5 years reported pain and/or dyspareunia. (Demirci F, Yucel O, Eren S, Alkan A, Demirci E, Yildirim U. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001;51(4):243-7.)

In addition, some plaintiffs' experts misconstrue the published data on mid-urethral sling complications, contending, for instance, that "[e]arly studies showed that the risk of bladder perforation during the procedure occurred 5-10% of [TVT] cases..." The actual overall risk of bladder perforation reported in recent systematic reviews and multi-center RCTs is approximately 3-5% with retropubic mid-urethral slings. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database of Systematic Reviews 2017; Schimpf MO, Rahn DD, Wheeler TL, et al. Sling surgery for stress urinary incontinence in women: a systematic review and metaanalysis. Am J Obstet Gynecol 2014; Richter, H.E., et al., Retropubic versus transobturator midurethral slings for stress incontinence. N Engl J Med, 2010. 362(22): p. 2066-76.)

Another example of a sweeping allegation made in the absence of data can be found in In Dr. Michael Margolis's May 2017 report which includes a whole section on potential complications of the TVT mesh (section IV C: The TVT Causes Infections and Greatly Enhances the Probability of Experiencing Serious, Resistant Infections). The entire section of his report has no published data to support the allegations. In fact, TVT sling procedures are associated with a decreased risk of infectious complications when compared with alternative procedures such as the Burch urethropexy or autologous facial sling procedures. In 2007, Albo reported that 93% of patients undergoing an autologous facial sling procedure and 61% of those undergoing a Burch procedure had post-operative urinary tract infections and approximately 3.6% of patients had a wound complication requiring surgical intervention. (Albo, M, et al. Burch Colposuspension versus Fascial Sling to Reduce Urinary Stress incontinence. N Engl J Med 2007; 356:2143-2155.) The risk of infectious complication after TVT procedures in the published literature are, to my knowledge, all far below this.

I disagree with plaintiffs' experts' contentions that a sling made of a larger-pore, lighter-weight mesh would be a safer and equally effective alternative to the TVT device. I am unaware of any mid-urethral slings with a larger pore size or lighter weight than the TVT mesh. There are no mid-urethral slings made of Ultrapro mesh, there is no long-term data to support the efficacy of Ultrapro mesh use in the context of a mid-urethral sling. Complications such as dyspareunia and erosion can still occur with Ultrapro mesh use in pelvic surgery. (Milani AL, et al., Outcomes and predictors of failure of trocar-guided vaginal mesh surgery for pelvic organ prolapse. Am J

Obstet Gynecol 2012;206:440.e1-8; Quemener J, et al., Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months median follow-up outcomes. Eur J Obstet & Gynecol and Reprod Biol. 2014;175:194-98.) The TVT sling is only 1.1 cm wide, and the pores are approximately 1,300 µm wide, meaning there are approximately 8 pores across the width of the mesh. I am unaware of any data indicating that a larger-pore mesh—which would therefore have fewer than approximately 8 pores across the width of the sling, would be effective. Type I meshes are macroporous meshes with a pore size larger than 75 µm. (Amid PK, Classification of biomaterials and their related complications in Thus, the pores are approximately 17 times larger than necessary to be considered macroporous.

I have used mid-urethral slings such as the TVT device since the late 1990s, implanting approximately 2,000 mid-urethral slings overall. As noted above, I was also trained on the Burch procedure and on needle suspension procedures such as the Raz and Stamey procedures. Based on my experience using retropubic mid-urethral slings—including but not limited to the TVT device—as well as alternative surgeries, and based on my research and analysis of the published scientific literature regarding the surgical treatment of stress urinary incontinence, I do not think there were alternative surgical treatments are safer or more effective in treating stress urinary incontinence. The risks associated with the use of the TVT device are present with other stress incontinence surgeries such as the Burch procedure or autologous fascial sling procedures. The risk of mesh exposure or erosion is arguably unique to mesh-based surgeries, but suture exposures or graft exposures can occur with non-mesh-based procedures, too. Mid-urethral slings such as the TVT, in many aspects of patient recovery and post-procedure complications, seems to offer a safer approach to SUI treatment than the Burch procedure or autologous fascial sling procedures. (Ford AA, et al., Midurethral slings for treatment of stress urinary incontinence review. Neurourol Urodyn. 2019 May 26. Doi: 10.1002/nau.24030 [Epub ahead of print].)

VII. The TVT Instructions for Use ("IFU")

It is my opinion that the IFU accompanying the TVT device was adequate and allowed surgeons to safely use the device to treat SUI. The IFU notes that that it is not a comprehensive reference to surgical technique for correcting SUI, and that the device should be used only by physicians trained in the surgical treatment of SUI and specifically, in implanting the TVT device. The IFU provides detailed instructions on how to implant the device, it lists the indications for its use and the contraindications, and it sets forth a number of warnings, precautions, and adverse reactions, including but not limited to risks of infection, nerve injury, bowel injury, bladder injury, retropubic bleeding, dysuria, de novo detrusor instability, vessel injury, extrusion, erosion, fistula formation, inflammation, and urinary retention. The risks set forth in the IFU are consistent with those reflected in the published medical literature regarding mid-urethral sling use, as well as my experience using the slings.

The device's IFU, in my opinion, did not need to include mention of risks that are not supported by published medical literature, such as a risk of shrinkage, particle loss of clinical significance, fraying, roping/curling, cancer, inadequate pore size, heavy weight, or chronic foreign body reaction that is clinically significant. Nor did the IFU need, in my opinion, to include risks that are common knowledge among licensed pelvic floor surgeons, such as pain, pain with

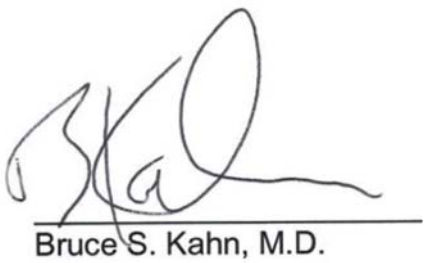
intercourse, or recurrent incontinence. (21 CFR Pt. 801.109.) Nor did the IFU, in my opinion, need to warn of the incidence of potential complications or how severe they may be. It is commonly known among surgeons that any surgical complication can be temporary or permanent, and any potential complication can be mild, moderate, or severe. (Ethicon Procedure re Creating and Revising Labeling, § 6.1.2 HMESH_ETH_11642462–81 (noting that device labeling "must convey the information that end-users need to safely use the device as intended by the manufacturer, taking into account the conditions of use and any issues that may be specific to the type of device."); AUGS Resident Learning Objectives ("Understand the difference between a pubovaginal and mi-urethral sling. Understand and perform a mid-urethral sling, using either a retropubic or trans-obturator approach."); FDA Device Labeling Guidance #G91-1, sec. VIII ("An adverse reaction is an undesirable effect, reasonably associated with the use of the device . . . ."); ABOG & ABU Guide to Learning in Female Pelvic Medicine and Reconstructive Surgery 2012 (fellows must be able to describe the intra and postoperative complications, and success following continence procedures including synthetic sling procedures, autologous fascial slings procedures, the MMK procedure, and the Burch procedure); ACGME Program Requirements for Graduate Medical Education in Female Pelvic Medicine and Reconstructive Surgery, sec. IV.A.5.b).(3) ("[C]ompleting the F3 year must demonstrate competence in their knowledge of: . . . complications, therapeutic procedures including surgery for: . . . urinary incontinence . . . .")

Ethicon also published the Surgeon's Resource Monograph to provide surgeons with expert opinions from a 17-surgeon panel on the use of the TVT device. The monograph provided guidance on patient selection, performance of the procedure, and the potential complications including vaginal bleeding, retropubic hematoma, vaginal perforation, difficulty placing the trocars, bladder perforations, voiding dysfunction, urethral injury, urethral erosion, mesh protrusion or defective healing, vascular injuries, bowel perforation, de novo urge, infection of the mesh, UTI, and device failure.

VIII. Conclusion

I hold the opinions set forth in this report to a reasonable degree of medical certainty. My opinions are based on my review of the depositions I have been provided, the materials listed on my reliance list, and upon my education, training, research, discussions with colleagues, and experience. I reserve the right to supplement or amend my report if I receive additional information.

Date: 6/20/19



Bruce S. Kahn, M.D.